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Task Force on Harmonisation of Classification and Labelling

Ad Hoc Expert Group on Target Organ Toxicity

ISSUE DOCUMENT NO 2 : CUT OFF VALUES

2nd Meeting of the ad hoc Expert Group on Target Organ Toxicity,
9th - 10th September 1999, Bethesda, Maryland, beginning at 9:30 a.m. on 9th September

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ISSUE DOCUMENT NO 2: CUT-OFF VALUES

ISSUE

1. A review of the existing systems shows that there are varying approaches to the classification criteria for target organ toxicity. Classification criteria vary from cut-offs based on dose to the use of professional judgement.

CURRENT PRACTICE

EU

2. The EU classification system uses a cut-off approach. As noted in the Detailed Review Document, cut-offs are used to create a complete and consistent system of classification.

3. The EU classification system for systemic target organ toxicity is fully implemented for new chemicals, based on animal studies (generally 90 day repeat dose studies). . Information from shorter (e.g. 28-day) or longer (e.g. 2-year) studies can be used for evaluation and in these cases extrapolation of the cut-off values is made to assess whether classification is justified. Some degree of expert judgement is also necessary in order to decide if the nature and severity of a particular effect should justify classification.

4. Dose cut off values are used in identifying the hazard of new chemicals. The rationale for this is that were this not done, virtually all new chemicals tested would be classified for target organ systemic toxicity, since test guidelines call for extending dosing until toxicity is seen. Existing chemicals are only partially classified since implementation of the EU classification system for existing chemicals is done on a time available basis. Since the frame of reference for the EU system is its implementation for new chemicals, any chemicals classified on the basis of human data (these chemicals are likely to be existing chemicals) would be prorated as to probable exposure related to the dose cut off values used for animal studies.

US

CPSC

5. CPSC's system calls for a weight of evidence approach to determine the potential of a substance to cause harm to humans. All available information from human and animal studies is identified and evaluated in identifying the hazard of consumer products. An assessment is then conducted to determine the likelihood of substantial harm to humans under expected conditions of exposure or reasonably foreseeable misuses of the product. Cut off values are not used for selecting hazard data.

6. In the US, CPSC mandates that likelihood of harm to humans be evaluated using a weight of evidence approach to all available hazard data, combined with consideration of likely exposures under conditions of use or probable misuse. Cut off values are not imposed on the hazard data thus used. However, even a set of chemicals which all showed some long-term toxicity in animal or human studies,

would not all be required to be labelled under this scheme because exposure is taken into account when estimating likelihood of harm.

7. OSHA The *Hazard Communication Standard* considers that there may be a target organ toxic effect if there is statistically significant evidence, based on at least one study conducted in accordance with established scientific principles. A weight of evidence approach is used for classification on the label whereas a single positive well-conducted study leads to identification on the MSDS. The Hazard Communication Standard is fully implemented in the US for existing chemicals as well as new industrial chemicals, based on available data. No cut off levels are specified for animal studies, epidemiology studies, or human incident data.

8. The US workplace system is fully implemented for all existing as well as new industrial chemicals, based on available data. OSHA does not require that specific studies be performed in laboratory animals, but when such data from appropriate sub-chronic or chronic studies are available, they should be used to identify hazardous chemicals. Much of the data and information on existing industrial chemicals is based on human incidents. Hazards thus identified have been substantiated to occur in humans under work place conditions. Because of workers' right to know, cut off values are not used.

Canada

WHMIS

9. Representatives of labour, industry and federal and provincial governments reached consensus that the criteria should be quantified to focus on those chemicals most likely to pose a hazard to workers.

10. The Canadian workplace system uses a cut-off approach but also allows professional judgement to be used to classify target organ toxic effects for new and existing chemicals. There is no direct relationship between animal data and human evidence. In WHMIS, all available evidence is considered in the classification for this endpoint. A single positive study, carried out in accordance with good scientific practices is sufficient for classification under WHMIS.

11. The cut-off approach in animal studies is considered reasonable given that some animal study protocols require effects to be seen, i.e., at very high doses. WHMIS regulations specify that animal evidence be derived from testing carried out in accordance with various guidelines such as those developed by the OECD, EPA, and FDA.

12. The Canadian workplace regulations also specify that a supplier may use information of which the supplier is aware or ought reasonably to be aware in place of the criteria. For example, a material for which there is valid documented evidence (epidemiological studies and case reports) based on established scientific principles that there is an adverse effect in humans following chronic exposure, is also sufficient for classification. In this case, adverse effects means injury to humans resulting from occupational exposure, including any reversible or irreversible impairment to health or irreversible diminished functional capacity. This allows for data to be considered in a situation where there is no recovery group and therefore, it cannot be determined if the effect is reversible or irreversible. When evaluating these types of studies, confounding factors must be considered such as concurrent exposure to other chemicals which may have contributed to the effects observed.

POSSIBLE APPROACHES IN DEVELOPING A HARMONIZED PROPOSAL

- Numerical Cut Off Approach
- Professional Judgement/Weight of Evidence used without Cut-offs
- Hybrid - Cut-off and Professional Judgement

13. Characterisation of target organ toxicity is based on significant effects occurring at or below a specific dose cut off value. This cut off value is referred to animal studies - typically the 90 day repeat dose study. Human data, when available, is used with a cut off referred to the dose cut off set for characterisation from animal studies. This provides an automatic way of screening chemicals based on animal testing and allows for equalisation of classification between animal and human data across chemicals.

14. Weight of evidence of all data, human incident, epidemiology, animal testing, is used to substantiate significant target organ toxicity effects which merit classification. This taps the considerable body of industrial toxicology data collected over the years. Weight of evidence determinations require that resources be expended, and there are no internationally recognised bodies classifying chemicals for target organ toxicity.

15. Evidence from human experience/incident is usually restricted to serious health consequences (clinical outcomes), whereas evidence from appropriate studies in animals can furnish much more detail from macroscopic and microscopic pathological examination - and this can often reveal hazards that may not be life-threatening but could be functionally impairing.

16. Hybrid - When a chemical is characterised only with animal data (typical of new chemicals, but also true for some existing chemicals), classification is based on a single dose cut off value.

17. When well-substantiated human data are available showing a target organ toxicity effect, the chemicals is classified, regardless of the level to which humans were likely to have been exposed. Positive human data, regardless of probable dose, predominates over animal data. Thus, if a new chemical is unclassified because no target organ toxicity was seen at or below a set dose level in animal testing, if subsequent human incident data become available showing a target organ toxicity effect, the chemical would be classified (regardless of the exposure level).

18. While positive human evidence can supercede negative evidence from studies in animals, the converse is not acceptable in view of the general limitations and unreliability of epidemiological studies.

DISCUSSION

19. If animal data are considered to be a screen, a dose level cut off for target organ toxicity can be considered to be a practical way to identify those chemicals most likely to give rise to target organ toxicity. If human data become available or were previously available, positive human data (well substantiated) would predominate and lead to classification. However, positive evidence from studies in animals is not superseded by negative human data.

20. Worker's right to know would be satisfied because the occurrence of incidents in humans indicates that both the toxicity potential was there and the use or misuse conditions led to manifestation of an effect. Further, if human incident data are available but animal testing has not occurred, animal testing need not be initiated to classify chemicals, thus saving laboratory animals.

CONSIDERATIONS

21. Cut off values for target organ toxicity are based on assessment of potential of injury to humans. The classification criteria for this endpoint is meant to identify the inherent properties of a chemical.

22. In EU, the 90 day repeat dose study is the basis for classification for target organ toxicity, with some chemicals characterised with a longer running subchronic study, perhaps 90 days.

Pros

23. The cut-off approach for target organ toxicity is consistent with the dose-response test used for acute toxicity. The chronic endpoints of carcinogenicity, mutagenicity, and reproductive toxicity are all or nothing effects which are generally irreversible and severe therefore a cut-off approach is not appropriate.

24. There should be a reasonable dose/concentration above which it would be accepted that all chemicals are potentially toxic. Repeated-dose studies in animals are designed to produce toxicity, even death, at the highest dose in order to test to the maximum - and so most studies will reveal toxic effects at least at the highest dose. Therefore, what is to be decided is not only what effects have been produced, but at what dose/concentration they were produced.

Cons

25. Target Organ toxicity includes a variety of health end points and certain countries find it challenging to justify cut off values for each health effect and possibly for each sector.

26. A cut off value approach will not be consistent with the criteria for other chronic end point already agreed upon. If the criteria for target organ toxicity are patterned after the GHS criteria for carcinogenicity, mutagenicity, and reproductive toxicity, cut off values would not be used.

ISSUES

27. Is it practical to use animal data for classification for the target organ endpoint without regard to cut off dosing values? For most workplace systems, wouldn't this be likely to lead to classification of most chemicals for which animal data are available? On the other hand, would imposition of a cut off value restrict workers' right to know?

28. If over classification would result if no numerical cut off value is used, wouldn't imposition of a cut off value mean that treatment of target organ toxicity is different from that of other chronic effects, since classification of oncogenicity and reproductive effects does not use cut off values?

29. If cut off values were to be used, how would they be chosen? A worker may be exposed to a chemical at several times and in many places in the work place in the course of a day. One could hypothesise levels equivalent to the highest likely levels of industrial chemicals under conditions of actual use. But how to account for multiple exposures? What about probable misuse levels?

30. If human incident data is compared, for likely exposure, to selected cut off values for animal studies, and certain chemicals thus implicated as hazardous are not classified, haven't we failed to inform workers of substantiated hazards?

How many industrial chemicals in use show not long-term effects at doses up to the limit dose of the tests